

T-cell reactivity of modified allergens

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The use of modified allergens such as allergoids for allergen-specific immunotherapy has been established for more than 10 years (1, 2). Allergoids are obtained by chemical modification of allergens with formaldehyde and glutaraldehyde. Their characteristic feature is minimal IgE-binding activity but retained immunogenicity (3). To gain further insight into the mechanisms of action of allergens and allergoids, we conducted *in vitro* investigations to assess the influence of concentration on proliferation and production of Th1 and Th2 cytokines from human T cells. With PBMC from both grass-pollen-allergic and nonallergic subjects, it could be demonstrated that the course of proliferation up to high concentrations was similar between allergen and allergoid. The typical Th1-cytokine IFN- γ was synthesized only with the highest concentrations of allergen and allergoid, whereas the typical Th2-cytokine IL-5 was produced even with very low antigen concentrations, reaching a maximum with a lower antigen concentration than IFN- γ . Compared with the native allergen, the allergoid led to lower production of both cytokines. The outcome of the response expressed as the IFN- γ /IL-5 ratio was similar for both preparations.

Similar studies were undertaken with TCL and TCC specific for the major allergen Phl p 5 from timothy grass pollen. As is usual in proliferation studies, autologous PBMC were used for antigen presentation. In this system, most of the TCL and TCC showed a more or less reduced reactivity with the allergoid as compared with the allergen. However, PBMC are not the principal target antigen-presenting cells (APC) reached during the course of SIT; instead, the principal target cells are dendritic cells (DC) and macrophages (M ϕ), which are the most potent APC in nonlymphoid tissues (4, 5). Therefore, investigations were extended to include DC and M ϕ generated from CD14⁺

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precursors from PBMC of the respective allergic subjects. GM-CSF and IL-4 were used to obtain DC [6, 7] and M-CSF to obtain M ϕ [8]. With these kinds of APC, a strong increase of the proliferation especially for the allergoid was obvious for all TCC tested. The degree of reactivity of a particular TCC with the allergoid in comparison with the native allergen depended on its epitope specificity and the allergic individual and was a reproducible feature with different batches of allergoid, demonstrating the conformity of allergoid production in terms of T-cell-stimulating activity. In contrast to DC and M ϕ , isolated B cells showed a strongly reduced activity concerning allergoid presentation. While B cells stimulated Th2 clones much more effectively than

Th1 clones with native allergen, all phenotypes were stimulated equally well after antigen presentation by DC and M ϕ .

The Th1 phenotype-promoting cytokine IL-12 [9, 10] was detectable in significant amounts only in supernatants of allergen-activated TCC and DC, the other types of APC did not give rise to any significant IL-12 production.

The results demonstrate that six-grass allergoids retain a highly reproducible T-cell-stimulating capacity when they are presented by professional APC such as DC and M ϕ . Therefore, allergoids are well suited for allergen-specific immunotherapy by T-cell targeting without provoking all the side-effects due to IgE reactivity.

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